

1001949



PATENT SPECIFICATION

NO DRAWINGS

1001949

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COMPLETE SPECIFICATION

Penetrating Agents

I, FRIEDRICH MEYER, of Schönewald Strasse 20, Hamburg-Wilhelmsburg, Germany, a German Citizen, do hereby declare the invention for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an ointment, liniment, lotion or like preparation for topical application.

A few decades ago, it was still widely believed that the outer skin of warm-blooded animals was completely impervious from the outside. Although it is now known that the skin does not provide absolutely complete protection against chemical influences—there are cases recorded in toxicology of medicinal poisoning caused by salicylic-acid-containing ointments and of industrial poisoning caused by alkyl phosphates and other contact insecticides—the skin is fairly impervious, and so only very small quantities are really absorbed when ointments, powders, jellies and liniments are applied externally in the conventional manner. The cosmetic, pharmaceutical or other active agents contained in such preparations permeate the epidermis, as a rule, either not at all or so slowly that there is almost no chance of being sure that there is any action in the deep layers of the skin (including the corium and subcutis). By far the majority of the quantity applied penetrates merely very superficially into the so-called pores—which are definitely not entrances—to be perhaps emulsified or subsequently removed by rubbing or washing. Reliable penetration of the epidermis (absorption into the skin) or percutaneous resorption into the general circulation (absorption through the skin), however, are exceptional, and the quantities concerned are small. Notwithstanding contrary statements, proof is seldom available of definite penetration or resorption. The ratio of the

quantity resorbed to the quantity applied is usually worse than 1:1000.

Since penetration of the epidermis occurs therefore either not at all or very slowly, many endeavours have been made to prolong the duration of the effect for days or even weeks. Most of the endeavours in this direction have been unsuccessful. Many appliances disclosed for this purpose do nothing more than retain the externally applied preparation at the place of action for as long as possible. This fact alone, however, shows that the rate of penetration or of resorption is very low. Detailed experiments by the Applicant have shown that the rate of resorption of the ordinary contents of ointments, jellies, liniments and other liquid or semi-solid preparations of active agents is very low if, indeed, it can be detected at all. Many hours or days pass before measurable quantities of active principle are absorbed.

The substances stated as vehicles, for instance, glycols, glycerin, ethanol or the like, are almost exclusively solvents or aids to solution. They have no effect either way on penetration and resorption. If an active agent can be percutaneously resorbed on its own, as can, for instance, some hormones, salicylic acid and some nicotinic acid esters, the penetration or resorption may be adequate provided that the duration of the action can be of the order of days. However, it is exceptional for such a long time to be available. Most cosmetic, pharmaceutical and other active agents cannot be resorbed percutaneously, at least not in practice, and cannot therefore on their own penetrate the epidermis.

According to the present invention there is provided an ointment, liniment, lotion or like preparation for topical application, comprising an active agent which is to penetrate the epidermis, and, as an aid for assisting penetration of said active agent into the epidermis, a monovalent saturated or unsaturated aliphatic,

[F]

5 cycloaliphatic or aromatic alcohol having from 4 to 12 carbon atoms; an aliphatic, cycloaliphatic or aromatic hydrocarbon having from 5 to 12 carbon atoms; a terpene having from 9 to 15 carbon atoms; an aliphatic, cycloaliphatic or aromatic aldehyde, ketone or ester having from 4 to 10 carbon atoms: an essential oil or a substance containing an essential oil; a halogenated or nitrated aliphatic, cycloaliphatic or aromatic hydrocarbon having from 2 to 8 carbon atoms; or a mixture of two or more of such penetration aids, and any inert carrier necessary for forming said preparation, the carrier being such or being present in an amount such as not to prevent penetration by said penetration aid.

10 The use of the aforesaid penetrating aids in such a preparation for topical application enables active agents to be introduced readily and rapidly into deep layers of the skin and, if required, enables active agents to be resorbed through the skin. The procedure to be described hereinafter therefore enables:

- 15 (a) active agents, not resorbable on their own, to be absorbed percutaneously, and
(b) the percutaneous absorption of difficultly or slowly resorbable active agents to be speeded up considerably.

The advantages of this are that:

- 20 1. The required duration of the action is only a matter of minutes.
2. The relatively deep layers of the skin are reached rapidly and reliably, and
3. the rate of penetration can be varied within wide limits and can therefore be readily adapted to suit particular requirements.

35 The present preparation for topical application is therefore based on using certain vehicle substances and resides in that, in addition to known aids to solution which are often wrongly called aids to resorption, and which may form at least part of the inert carrier, vehicle substances are used which produce or assist penetration of the epidermis or resorption by the skin. Aids to penetration and resorption are therefore used in addition to aids to solution. The dwell time of the active agents in the skin can be controlled within wide limits by an appropriate choice of penetrating aids or by mixing with an aid to solution which has no effect on resorption. If, as is not so common, the active agent is sufficiently soluble in the penetrating aid, there is, of course, no need to use a special aid to solution. The present preparations containing the active agents dissolved in them are applied conventionally by being rubbed or massaged in or just by contact; in the case of liquid, an impregnated cotton wool pad with or without a cover can be used.

60 Conventional solvents, such as glycols, glycerin, ethanol or water, can usually be used. The following compounds are very suitable as penetrating aids:

- 65 1. Monovalent, saturated and unsaturated

aliphatic cycloaliphatic and aromatic alcohols having a total of from 4 to 12 carbon atoms, for instance, hexanol, hexenol, cyclohexanol and benzyl alcohol (N.B.—*monovalent*, secondary, tertiary and polyvalent alcohols are aids to solution rather than penetrating agents);

2. Aliphatic, cycloaliphatic and aromatic hydrocarbons having from 5 to 12 carbon atoms, for instance, hexane, hexene, cyclohexane and isopropylbenzene;

3. Terpenes having from 9 to 15 carbon atoms, for instance, thymene and 1-pinene;

4. Aliphatic, cycloaliphatic and aromatic aldehydes and ketones having from 4 to 10 carbon atoms, for instance, heptylaldehyde, cyclohexanone and benzaldehyde;

5. Aliphatic cycloaliphatic and aromatic esters having from 4 to 10 carbon atoms, for instance, isoamylacetate and benzylpropionate;

6. Essential oils or substances containing them, for instance, *Ol. eucalypti*, *Ol. Rutae*, cumin oil, limonene, thymol, fenchone and carbene;

7. Halogenated or nitrated aliphatic, cycloaliphatic and aromatic hydrocarbons having 2 to 8 carbon atoms, for instance, hexylbromide, hexylchloride, cyclohexylchloride, benzylchloride, o-dichlorobenzene and nitrocyclohexane; and

8. Mixtures or solutions of all these compounds.

It is to be noted that some of the chlorinated hydrocarbons included under (7) above are toxic or are skin irritants and care should be employed in using them, although they may be of use where an irritant action on the skin is required.

It is to be appreciated that the penetrating effect of the penetrating aids mentioned above is not equal and varies considerably from those which have a strong penetrating effect to those which have a weak penetrating effect, that is to say they require very long periods of contact with the skin to effect penetration.

The active agent of the present preparation for topical application may be a cosmetic agent, a pharmaceutical agent, such as tetracycline, or a dye, or pigment or any other agent which it is desired to introduce into the epidermis. In preparing the preparation, the active agent and penetrating agent are selected preferably so that the active agent is soluble in the penetrating agent, and such that the solution of active agent and penetrating agent is stable. If desired, or if the active agent is not readily soluble in the penetrating agent, a solvent aid may be added which may form part of the carrier.

If it is desired to prepare a non-liquid preparation, such as an ointment, then the above solution can be turned into a jelly or unguent by known pharmaceutical techniques such as by adding a thickner, e.g. fumed silica, or an unguent base. However, it must be borne in

mind that thickeners or unguent bases may reduce the penetration rate, although this may not be of disadvantage if the penetrating aid has such a high rate of penetration that it is desirable to control the rate of penetration.

- 5 In general, fatty unguent bases should be avoided as they have an inhibiting effect on the penetrating aid, although, as indicated, they may be useful in controlling the rate of penetration. Thus, it is preferred not to use unguent bases such as liquid paraffin, solid paraffin, petroleum jelly, olive oil, glycerine, *Adeps lanae anhydrous*, lanolin, *Adeps suillus*, stearyl alcohol, cetyl alcohol and zinc ointment bases.

15 The invention will now be illustrated by the following Examples.

EXAMPLE 1

- 20 Malachite green, which is very easy to recognise in the skin as a pigment and which therefore permits of ready histological identification in a frozen section, has strong fungicidal properties ("active principle"). Malachite green dissolved in ethyl glycol does not penetrate the epidermis, but when cyclohexane is used as a penetrating agent in addition to malachite green, which is an aid to solution, malachite green can definitely be detected in deep layers of the skin (corium) after a few minutes. The rate of penetration increases rapidly as the proportion of cyclohexane increases.

EXAMPLE 2

- 35 A fluorescing pigment, Rhodamine B, acting as a model for any active principle, is not absorbed from an ethanolic or aqueous solution nor after solution in ethyl glycol, propylene glycol or glycerin. When a penetrating agent is added to these aids to solution, a deep penetration results from a short contact. For instance, if as little as 10% of cyclohexane is added to a Rhodamine B solution in ethyl glycol, the pigment is visible in deep layers of the skin after as little as thirty minutes later. When 40 50% of cyclohexane is added, Rhodamine is detected in the corium after as little as three minutes; after ten minutes it can be detected even in the subcutaneous fatty tissue.

- 50 However, if a mixture of cyclohexanone and Rhodamine B is applied, the Rhodamine

B does not appear in the corium because it is not sufficiently soluble in cyclohexane.

EXAMPLE 3

The following Table lists the results obtained with various penetrating agents:

KEY TO TABLE

| | |
|---|----|
| Column 1: Penetrating agent—substances tested as to their penetrating agent properties. | |
| Column 2: L% = addition (in percentage by volume) of an aid to solution which has no effect on penetrating properties. Usually ethylglycol (see page 2 of table). | 60 |
| 50 = 50% of aid to solution. | |
| — = without any addition. | |
| Column 3: Active principle: | 65 |
| Ma = malachite green | |
| Rh = Rhodamine B | |
| Or = Orcein | |
| Mb = Methylene blue | |
| Su = Sudan III | 70 |
| Ac = Acridine orange | |
| Na = Sodium fluorescein | |
| Fl = Fluorescein | |
| Eo = Eosin | |
| Ha = Harmine | 75 |
| Fu = Fuchsine | |
| Er = Erythrosine | |
| Sa = Safranine | |
| To = Toluidine blue | |
| Ge = Gentian violet. | 80 |
| Column 4: t = duration of action in minutes (') or hours (h). | |
| Column: Epithelium | |
| Column 6: Hair follicles | |
| Column 7: Corium | 85 |
| Column 8: Subcutis | |

HISTOLOGICAL FINDINGS

| | |
|--|----|
| + strong colouring or fluorescence | |
| (+) noticeable colouring or fluorescence | |
| = slight colouring or fluorescence | 90 |
| — no colouring or fluorescence | |

There is genuine penetration only when the active principle can be detected in the corium (column 7 or in the subcutis (column 8).

Column 9: Remarks.

The findings were made on guinea pigs unless other wise specified in column 9.

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75

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85

90

95

| Penetrating Agent | L % | Active substance | t | Epithelium | Hair shafts | Corium | Subcutis | Remarks |
|-------------------|-----|------------------|-----|------------|-------------|--------|----------|---------|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Methanol | — | Ma | 2h | + | — | — | — | |
| Ethanol | — | Ma | 2h | = | — | — | — | |
| Ethanol | — | Ma | 24h | = | — | — | — | |
| Ethanol | — | Rh | 3 h | = | — | — | — | |
| n-Propanol | — | Ma | 2h | — | — | — | — | |
| i-Propanol | — | Ma | 2h | — | — | — | — | |
| n-Butanol | 50 | Ma | 2h | = | = | — | — | |
| n-Butanol | 50 | Ma | 20h | = | (+) | = | — | |
| i-Butanol | 50 | Ma | 2h | = | = | — | — | |
| tert. Butanol | 50 | Ma | 2h | = | — | — | — | |
| n-Pentanol | 50 | Ma | 2h | (+) | (+) | = | — | |
| i-Amylalcohol | 50 | Ma | 2h | (+) | (+) | = | — | |
| 3-Pentanol | 50 | Ma | 2h | (+) | (+) | = | — | |
| n. prim. Hexanol | 50 | Ma | 2h | + | + | + | = | |
| " | — | Rh | 2h | + | + | + | + | |
| " | — | Rh | 5' | = | = | — | — | Cat |
| " | — | Rh | 30' | (+) | (+) | = | — | Cat |
| " | — | Rh | 2h | + | + | (+) | = | Rabbit |
| " | — | Rh | 30' | (+) | (+) | (+) | = | |
| n-Heptanol | 50 | Ma | 2h | + | + | + | (+) | |
| prim. Octanol | 50 | Ma | 2h | + | + | (+) | = | |
| sec. Octanol | 50 | Ma | 2h | (+) | (+) | = | — | |
| Nonylalcohol | 50 | Ma | 2h | + | + | + | + | |
| Decylalcohol | 50 | Ma | 2h | + | + | + | + | |
| Dodecylalcohol | 50 | Ma | 2h | + | + | + | = | |
| n. prim. | 50 | Rh | 2h | + | + | + | + | |
| Hexene(3)ol(1) | 50 | Rh | 2h | + | (+) | (+) | = | |
| Heptene(3)ol(1) | 50 | Rh | 2h | + | (+) | = | = | |
| Cyclohexanol | 50 | Rh | 2h | (+) | (+) | = | — | |
| Benzylalcohol | 50 | Rh | 2h | (+) | (+) | = | — | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-------------------------------|----|----|-----|-----|-----|-----|---|------------------|
| Phenylmethyl-alcohol | 50 | Rh | 2h | — | — | — | — | |
| Phenylethyl-alcohol | 50 | Rh | 2h | — | — | — | — | |
| Methylglycol | 50 | Rh | 2h | = | — | — | — | |
| Methylglycol | — | Rh | 2h | = | — | — | — | |
| Ethylglycol | — | Ma | 2h | = | — | — | — | |
| „ | — | Ma | 20h | = | = | — | — | |
| „ | — | Rh | 2h | = | — | — | — | see Example 2 |
| „ | — | Rh | 2h | = | — | — | — | Dog |
| „ | — | Rh | 2h | = | — | — | — | Rabbit |
| „ | — | Rh | 2h | — | — | — | — | Cat |
| „ | — | Mb | 2h | — | — | — | — | |
| „ | — | Mb | 6h | — | — | — | — | |
| „ | — | Or | 2h | = | = | — | — | |
| Ethyleneglycol | — | Rh | 2h | — | — | — | — | |
| 1,2-propylene glycol | — | Rh | 2h | = | — | — | — | |
| 1,3-butyleneglycol | — | Rh | 2h | = | — | — | — | |
| Carbitol | — | Rh | 2h | = | = | — | — | |
| Hexamethylene glycol | 50 | Rh | 2h | = | — | — | — | |
| Glycerin | 50 | Rh | 2h | = | = | — | — | |
| Geraniol | 50 | Rh | 2h | — | — | — | — | |
| Linalool | 50 | Rh | 2h | — | — | — | — | |
| Terpinol hydrate | 90 | Rh | 2h | — | — | — | — | |
| Terpineol, thickly viscous | 50 | Rh | 2h | (+) | (+) | = | — | |
| Terpineol, fresh | 50 | Rh | 2h | + | (+) | (+) | — | |
| Menthol | 50 | Rh | 2h | = | = | = | — | |
| Eucalyptol | 50 | Rh | 2h | + | + | (+) | = | |
| Cumin alcohol | 50 | Rh | 2h | = | = | — | — | |
| Anethole | 50 | Rh | 2h | — | — | — | — | |
| Eugenol | 50 | Rh | 2h | — | — | — | — | |
| Isoeugenol | 50 | Rh | 2h | — | — | — | — | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-----------------|----|----|-----|-----|-----|---|---|---|
| Isoeugenol | — | Rh | 2h | — | — | — | — | |
| Carvacrol | 50 | Rh | 2h | — | — | — | — | |
| Apiole | 50 | Rh | 2h | — | — | — | — | |
| Safrol | 50 | Rh | 2h | = | = | — | — | |
| Tinct. Aloes | — | Rh | 2h | = | — | — | — | |
| „ Colocynthid. | — | Rh | 2h | = | — | — | — | |
| „ Cantharidis | — | Rh | 2h | = | — | — | — | |
| „ Capsioi | — | Rh | 2h | = | — | — | — | |
| Spirit. Sinapis | — | Rh | 2h | = | — | — | — | |
| Pentane | 50 | Rh | 2h | + | + | + | + | |
| Hexane | 50 | Rh | 2h | + | + | + | + | |
| Heptane | 50 | Rh | 2h | + | + | + | + | |
| Pentene (2) | 50 | Rh | 2h | + | + | + | + | |
| Hexene (1) | 50 | Rh | 2h | + | + | + | = | |
| Heptene (1) | 50 | Rh | 2h | + | + | + | + | |
| Octene (1) | 50 | Rh | 2h | + | + | + | + | |
| Nonene (1) | 50 | Rh | 2h | + | + | + | + | |
| Decene (1) | 50 | Rh | 2h | + | + | + | + | |
| Cyclohexane | — | Rh | 10' | = | = | = | = | |
| „ | — | Rh | 30' | = | (+) | = | = | |
| „ | — | Or | 30' | = | — | — | — | |
| „ | — | Or | 3h | = | = | — | — | |
| „ | — | Mb | 2h | = | = | — | — | |
| „ | — | Mb | h | = | = | — | — | |
| „ | 20 | Or | 2h | (+) | + | = | = | |
| „ | 25 | Rh | 10' | + | + | + | + | |
| „ | 25 | Rh | 30' | + | + | + | + | |
| „ | 25 | Or | 30' | + | + | = | = | |
| „ | 25 | Or | 1h | + | + | + | + | |
| „ | 25 | Mb | 2h | = | = | = | — | |
| „ | 25 | Ma | 1h | = | (+) | = | — | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-------------|----|----|-----|-----|-----|-----|-----|--------|
| Cyclohexane | 25 | Rh | 30' | + | + | (+) | = | Dog |
| " | 25 | Rh | 30' | + | + | = | = | Cat |
| " | 25 | Rh | 60' | + | + | + | + | Cat |
| " | 40 | Ma | 1h | + | (+) | = | - | |
| " | 50 | Ma | 1h | + | + | + | = | |
| " | 50 | Ma | 2h | + | + | = | = | |
| " | 50 | Su | 2h | + | + | = | = | |
| " | 50 | Or | 1h | + | + | + | = | |
| " | 50 | Ac | 30' | + | + | (+) | = | |
| " | 50 | Ac | 1h | + | + | (+) | = | |
| " | 50 | Na | 30' | + | + | (+) | = | |
| " | 50 | Na | 1h | + | + | + | = | |
| " | 50 | Fl | 30' | (+) | = | - | - | |
| " | 50 | Fl | 1h | (+) | = | (+) | = | |
| " | 50 | Eo | 1h | + | + | + | + | |
| " | 50 | Rh | 2h | = | = | = | - | |
| " | 50 | Rh | 5' | + | + | (+) | (+) | |
| " | 50 | Rh | 10' | + | + | + | + | |
| " | 50 | Rh | 30' | + | + | + | + | |
| " | 50 | Rh | 1h | + | + | + | + | |
| " | 50 | Rh | 30' | + | + | = | = | Dog |
| " | 50 | Rh | 1h | + | + | + | + | Dog |
| " | 50 | Rh | 30' | + | + | = | = | Cat |
| " | 50 | Rh | 10' | (+) | (+) | (+) | (+) | Rabbit |
| " | 50 | Rh | 30' | + | + | + | + | Rabbit |
| " | 50 | Rh | 90' | + | + | + | + | Rabbit |
| " | 50 | Ha | 30' | + | + | (+) | = | Dog |
| " | 50 | Ha | 30' | + | + | (+) | (+) | |
| " | 50 | Ha | 10' | = | = | - | - | |
| " | 75 | Ma | 1h | + | + | + | = | |
| " | 75 | Ma | 2h | + | + | (+) | (+) | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---------------------|----|----|-----|-----|-----|-----|-----|-----|
| Cyclohexane | 75 | Fu | 2h | + | + | (+) | (+) | |
| " | 75 | Er | 2h | + | + | (+) | (+) | |
| " | 75 | Sa | 2h | + | + | (+) | = | |
| " | 75 | Ge | 2h | + | + | (+) | - | |
| " | 75 | To | 2h | + | + | = | = | |
| " | 75 | Or | 30' | + | + | (+) | = | |
| " | 75 | Or | 3h | + | + | + | (+) | |
| " | 75 | Rh | 2' | (+) | (+) | = | - | |
| " | 75 | Rh | 5' | + | (+) | (+) | = | |
| " | 75 | Rh | 10' | (+) | (+) | (+) | (+) | |
| " | 75 | Rh | 30' | + | + | + | + | |
| " | 75 | Rh | 2h | + | + | + | + | |
| " | 75 | Rh | 30' | + | + | = | = | Dog |
| " | 75 | Rh | 30' | + | + | = | | Cat |
| " | 80 | Or | 1h | (+) | + | (+) | - | |
| " | 80 | Rh | 1h | + | + | + | = | |
| " | 90 | Rh | 1h | + | + | (+) | = | |
| Methyl-cyclohexane | 50 | Rh | 2h | + | + | + | + | |
| Benzene | 50 | Rh | 2h | + | + | + | = | |
| Toluene | 50 | Rh | 2h | + | + | + | (+) | |
| Paracymene | 50 | Rh | 2h | + | + | + | = | |
| Cumene | 50 | Rh | 2h | + | + | (+) | = | |
| Limonene | 50 | Rh | 1h | (+) | (+) | = | - | |
| 1,2-diethoxy-ethene | 50 | Rh | 2h | (+) | = | - | - | |
| 1,2-dibutoxy-ethene | 50 | Rh | 2h | + | + | + | + | |
| Hexalkoxy-ethane | 50 | Rh | 2h | - | - | - | - | |
| Dimethoxy-ethane | 50 | Rh | 2h | (+) | = | - | - | |
| Oleum Rutae | 50 | Rh | 1h | + | + | (+) | (+) | |
| Cumin oil | 50 | Rh | 1h | + | + | (+) | (+) | |
| Ol.Menth. | 50 | Rh | 1h | + | + | (+) | (+) | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|----------------------------|----|----|----|-----|-----|-----|-----|---|
| Ol.Eucalypti | 50 | Rh | 1h | + | + | (+) | (+) | |
| Ol.Galangae | 50 | Rh | 1h | + | (+) | = | = | |
| Ol.Tanaceti | 50 | Rh | 1h | (+) | (+) | = | = | |
| Peppermint oil | 50 | Rh | 1h | (+) | (+) | (+) | - | |
| Ol.Camphoric | 50 | Rh | 1h | (+) | (+) | = | = | |
| Ol.Sabinae | 50 | Rh | 1h | = | = | = | = | |
| Ol.Pini sibir. | 50 | Rh | 1h | = | = | = | - | |
| Ol.Menth.pip. | 50 | Rh | 1h | (+) | = | = | - | |
| Ol.Terebinth. | 50 | Rh | 1h | (+) | (+) | = | - | |
| „ | 50 | Rh | 2h | + | + | + | (+) | |
| Ol.Juniperi | 50 | Rh | 1h | = | = | = | - | |
| Ol.Petrosel. | 50 | Rh | 1h | = | = | - | - | |
| Ol.Thymi | 50 | Rh | 1h | = | = | - | - | |
| Ol.Balsami } Copaivae } | 50 | Rh | 1h | = | = | - | - | |
| Sassafras oil. | 50 | Rh | 2h | (+) | (+) | - | - | |
| Ol. Anisi | 50 | Rh | 1h | - | - | - | - | |
| Peru balsam | 50 | Rh | 1h | - | - | - | - | |
| Ol.Calami | 50 | Rh | 1h | - | - | - | - | |
| Patchioul oil | 50 | Rh | 1h | - | - | - | - | |
| Ol.Pagi ethen. | 50 | Rh | 1h | - | - | - | - | |
| Tolu oil. | 50 | Rh | 1h | - | - | - | - | |
| Ol. Pimentae | 50 | Rh | 1h | - | - | - | - | |
| Ol. Origani } orotici } | 50 | Rh | 1h | - | - | - | - | |
| Ajowan oil. | 50 | Rh | 1h | - | - | - | - | |
| Ol. Spicae | 50 | Rh | 1h | - | - | - | - | |
| Thymene(1-Pinene) | 50 | Rh | 1h | + | + | (+) | (+) | |
| α -Pinene | 50 | Rh | 1h | (+) | + | (+) | | |
| Propionaldehyde | 50 | Rh | 1h | = | = | - | - | |
| Butylaldehyde | 50 | Rh | 1h | = | = | - | - | |
| Hexylaldehyde | 50 | Rh | 2h | = | = | = | - | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-------------------------------------|----|----|----|-----|-----|-----|---|---|
| Heptylaldehyde | 50 | Rh | 2h | = | = | = | = | |
| Octylaldehyde | 50 | Rh | 2h | = | = | — | — | |
| Nonylaldehyde | 50 | Rh | 2h | = | = | — | — | |
| n-capronaldehyde | 50 | Rh | 2h | = | = | — | — | |
| Cyclohexanone | 50 | Rh | 2h | = | = | = | — | |
| Butanone | 50 | Rh | 2h | = | — | — | — | |
| Methylaceto-phenone | 50 | Rh | 2h | = | = | — | — | |
| Methylheptyl-ketone | 50 | Rh | 2h | = | = | = | — | |
| Methylnonyl-ketone | 50 | Rh | 2h | (+) | (+) | = | — | |
| Citral | 50 | Rh | 2h | = | = | — | — | |
| Citronellal | 50 | Rh | 2h | = | — | — | — | |
| Pulegone | 50 | Rh | 2h | (+) | (+) | = | = | |
| Thujone | 50 | Rh | 2h | = | = | = | — | |
| Fenchone | 50 | Rh | 2h | = | = | — | — | |
| Carvon | 50 | Rh | 2h | = | = | = | — | |
| Cumaldehyde | 50 | Rh | 2h | = | = | — | — | |
| Cinnemal | 50 | Rh | 2h | = | — | — | — | |
| Acetone | 50 | Rh | 2h | = | — | — | — | |
| Dioxane | 50 | Rh | 2h | = | — | — | — | |
| Acetylacetate | 50 | Rh | 2h | = | = | — | — | |
| i.amylacetate | 50 | Rh | 2h | (+) | (+) | (+) | — | |
| n-octylacetate | 50 | Rh | 2h | = | = | — | — | |
| Triacetate } glycerol } | 50 | Rh | 2h | = | — | — | — | |
| Acetoacetic acid } ethyl ester } | 50 | Rh | 2h | = | — | — | — | |
| Benzyl acetate | 50 | Rh | 2h | = | = | = | — | |
| Benzyl propionate | 50 | Rh | 2h | (+) | = | — | — | |
| Benzyl butyrate | 50 | Rh | 2h | (+) | = | = | — | |
| Benzyl benzoate | 50 | Rh | 2h | = | = | — | — | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---------------------------------|----|----|----|-----|-----|-----|-----|---|
| Salicylic methyl acid ester | 50 | Rh | 2h | = | = | — | — | |
| Salicylic amyl ester | 50 | Rh | 2h | = | — | — | — | |
| Benzoic acid ethyl ester | 50 | Rh | 2h | = | = | — | — | |
| Phenyl acetic acid methyl ester | 50 | Rh | 2h | = | — | — | — | |
| Phenyl acetic acid ethyl ester | 50 | Rh | 2h | = | — | — | — | |
| Phenylethyl-acetate | 50 | Rh | 2h | = | = | — | — | |
| p-cresolmethyl ether | 50 | Rh | 2h | = | = | = | — | |
| p-cresoethyl-ether | 50 | Rh | 2h | = | = | = | — | |
| Diphenyl ether | 50 | Rh | 2h | = | = | — | — | |
| Dimethyl phthalate | 50 | Rh | 2h | = | — | — | — | |
| Menthyl-valerianate | 50 | Rh | 2h | = | = | = | — | |
| Geranyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Geranyl formiate | 50 | Rh | 2h | = | = | = | — | |
| Geranyl propionate | 50 | Rh | 2h | = | = | = | — | |
| Geranyl butyrate | 50 | Rh | 2h | = | = | — | — | |
| Linalyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Terpinyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Fenchyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Sabinol acetate | 50 | Rh | 2h | = | = | — | — | |
| Bornyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Benzyl cinnamate | 50 | Rh | 2h | = | — | — | — | |
| n-valeric acid diethyl amide | 50 | Rh | 2h | = | — | — | — | |
| Dichloro-ethylene | 50 | Rh | 2h | (+) | (+) | = | = | |
| Trichloroethylene | 50 | Rh | 2h | (+) | (+) | = | = | |
| Tetrachloroethylene | 50 | Rh | 2h | (+) | (+) | = | — | |
| n-allyl bromide | 50 | Rh | 2h | + | + | + | + | |
| n-allyl chloride | 50 | Rh | 2h | + | + | (+) | = | |
| Dibromo ethane | 50 | Rh | 2h | + | + | (+) | (+) | |
| Dichloro ethane | 50 | Rh | 2h | + | + | (+) | (+) | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|----------------------------------|----|----|----|-----|-----|-----|-----|---|
| Tetrachloro-ethane | 50 | Rh | 2h | (+) | (+) | = | = | |
| Tetrabromo ethane | 50 | Rh | 2h | (+) | (+) | = | - | |
| n-butyl bromide | 50 | Rh | 2h | (+) | (+) | = | - | |
| n-amylbromide | 50 | Rh | 2h | (+) | (+) | = | = | |
| sec. amyl bromide | 50 | Rh | 2h | (+) | (+) | (+) | = | |
| n-hexyl bromide | 50 | Rh | 2h | = | + | (+) | (+) | |
| n-heptyl bromide | 50 | Rh | 2h | + | + | (+) | = | |
| n-octyl bromide | 50 | Rh | 2h | (+) | (+) | = | = | |
| i-butylene bromide | 50 | Rh | 2h | (+) | (+) | (+) | - | |
| Cyclohexyl chloride | 50 | Rh | 2h | + | + | + | + | |
| n-dichloro benzene | 50 | Rh | 2h | + | (+) | (+) | (+) | |
| Benzyl chloride | 50 | Rh | 2h | = | = | = | - | |
| 1-chloro-1,2-di-ethoxyethene | 50 | Rh | 2h | + | + | + | + | |
| 1,2-dichloro-1,2-diethoxy-ethene | 50 | Rh | 2h | + | + | + | + | |
| Ethyl-chlorhydrin | 50 | Rh | 2h | = | - | - | - | |
| Nitromethane | 50 | Rh | 2h | = | - | - | - | |
| Nitroethane | 50 | Rh | 2h | = | - | - | - | |
| 1-nitropropane | 50 | Rh | 2h | = | - | - | - | |
| 2-nitropropane | 50 | Rh | 2h | (+) | - | - | - | |
| Nitrocyclohexane | 50 | Rh | 2h | + | + | + | (+) | |
| α -picoline | 50 | Rh | 2h | - | - | - | - | |
| 2,4-lutidine | 50 | Rh | 2h | - | - | - | - | |
| Paraffinum liquid | 50 | Rh | 2h | = | - | - | - | |
| Yellow paraffin jelly | 50 | Rh | 2h | - | - | - | - | |
| Yellow paraffin oil | 50 | Rh | 2h | - | - | - | - | |
| Oleum Olivarum | 50 | Rh | 2h | = | - | - | - | |
| Ol. Arachidis. | 50 | Rh | 2h | = | - | - | - | |
| Ol. Amygdalarum | 50 | Rh | 2h | = | - | - | - | |
| OLJecoris Aselli. | 50 | Rh | 2h | = | - | - | - | |

1001949



PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Penetrating Agents

I, FRIEDRICH MEYER, of Schönewaldter
Strasse 20, Hamburg-Wilhelmsburg, Ger-
many, a German Citizen, do hereby declare
the invention for which I pray that a patent
may be granted to me, and the method by
which it is to be performed, to be particularly
described in and by the following state-
ment:—

This invention relates to an ointment, lini-
ment, lotion or like preparation for topical
application.

A few decades ago, it was still widely be-
lieved that the outer skin of warm-blooded
animals was completely impervious from the
outside. Although it is now known that the
skin does not provide absolutely complete pro-
tection against chemical influences—there are
cases recorded in toxicology of medicinal
poisoning caused by salicylic-acid-containing
ointments and of industrial poisoning caused
by alkyl phosphates and other contact insecti-
cides—the skin is fairly impervious, and so
only very small quantities are really absorbed
when ointments, powders, jellies and liniments
are applied externally in the conventional
manner. The cosmetic, pharmaceutical or
other active agents contained in such prepar-
ations permeate the epidermis, as a rule, either
not at all or so slowly that there is almost
no chance of being sure that there is any action
in the deep layers of the skin (including the
corium and subcutis). By far the majority of
the quantity applied penetrates merely very
superficially into the so-called pores—which
are definitely not entrances—to be perhaps
emulsified or subsequently removed by rub-
bing or washing. Reliable penetration of the
epidermis (absorption into the skin) or per-
cutaneous resorption into the general circula-
tion (absorption through the skin), however,
are exceptional, and the quantities concerned
are small. Notwithstanding contrary state-
ments, proof is seldom available of definite
penetration or resorption. The ratio of the

quantity resorbed to the quantity applied is
usually worse than 1:1000.

Since penetration of the epidermis occurs
therefore either not at all or very slowly, many
endeavours have been made to prolong the
duration of the effect for days or even weeks.
Most of the endeavours in this direction have
been unsuccessful. Many appliances disclosed
for this purpose do nothing more than retain
the externally applied preparation at the place
of action for as long as possible. This fact
alone, however, shows that the rate of pene-
tration or of resorption is very low. Detailed
experiments by the Applicant have shown
that the rate of resorption of the ordinary
contents of ointments, jellies, liniments and
other liquid or semi-solid preparations of
active agents is very low if, indeed, it can be
detected at all. Many hours or days pass be-
fore measurable quantities of active principle
are absorbed.

The substances stated as vehicles, for in-
stance, glycols, glycerin, ethanol or the like,
are almost exclusively solvents or aids to
solution. They have no effect either way on
penetration and resorption. If an active agent
can be percutaneously resorbed on its own,
as can, for instance, some hormones, salicylic
acid and some nicotinic acid esters, the pene-
tration or resorption may be adequate pro-
vided that the duration of the action can be
of the order of days. However, it is exceptional
for such a long time to be available. Most
cosmetic, pharmaceutical and other active
agents cannot be resorbed percutaneously, at
least not in practice, and cannot therefore on
their own penetrate the epidermis.

According to the present invention there is
provided an ointment, liniment, lotion or like
preparation for topical application, comprising
an active agent which is to penetrate the epi-
dermis, and, as an aid for assisting penetration
of said active agent into the epidermis, a
monovalent saturated or unsaturated aliphatic,

[F]

cycloaliphatic or aromatic alcohol having from 4 to 12 carbon atoms; an aliphatic, cycloaliphatic or aromatic hydrocarbon having from 5 to 12 carbon atoms; a terpene having from 9 to 15 carbon atoms; an aliphatic, cycloaliphatic or aromatic aldehyde, ketone or ester having from 4 to 10 carbon atoms: an essential oil or a substance containing an essential oil; a halogenated or nitrated aliphatic, cycloaliphatic or aromatic hydrocarbon having from 2 to 8 carbon atoms; or a mixture of two or more of such penetration aids, and any inert carrier necessary for forming said preparation, the carrier being such or being present in an amount such as not to prevent penetration by said penetration aid.

The use of the aforesaid penetrating aids in such a preparation for topical application enables active agents to be introduced readily and rapidly into deep layers of the skin and, if required, enables active agents to be resorbed through the skin. The procedure to be described hereinafter therefore enables:

- (a) active agents, not resorbable on their own, to be absorbed percutaneously, and
- (b) the percutaneous absorption of difficultly or slowly resorbable active agents to be speeded up considerably.

The advantages of this are that:

1. The required duration of the action is only a matter of minutes.
2. The relatively deep layers of the skin are reached rapidly and reliably, and
3. the rate of penetration can be varied within wide limits and can therefore be readily adapted to suit particular requirements.

The present preparation for topical application is therefore based on using certain vehicle substances and resides in that, in addition to known aids to solution which are often wrongly called aids to resorption, and which may form at least part of the inert carrier, vehicle substances are used which produce or assist penetration of the epidermis or resorption by the skin. Aids to penetration and resorption are therefore used in addition to aids to solution. The dwell time of the active agents in the skin can be controlled within wide limits by an appropriate choice of penetrating aids or by mixing with an aid to solution which has no effect on resorption. If, as is not so common, the active agent is sufficiently soluble in the penetrating aid, there is, of course, no need to use a special aid to solution. The present preparations containing the active agents dissolved in them are applied conventionally by being rubbed or massaged in or just by contact; in the case of liquid, an impregnated cotton wool pad with or without a cover can be used.

Conventional solvents, such as glycols, glycerin, ethanol or water, can usually be used.

The following compounds are very suitable as penetrating aids:

1. Monovalent, saturated and unsaturated

aliphatic cycloaliphatic and aromatic alcohols having a total of from 4 to 12 carbon atoms, for instance, hexanol, hexenol, cyclohexanol and benzyl alcohol (N.B.—monovalent, secondary, tertiary and polyvalent alcohols are aids to solution rather than penetrating agents);

2. Aliphatic, cycloaliphatic and aromatic hydrocarbons having from 5 to 12 carbon atoms, for instance, hexane, hexene, cyclohexane and isopropylbenzene;

3. Terpenes having from 9 to 15 carbon atoms, for instance, thymene and 1-pinene;

4. Aliphatic, cycloaliphatic and aromatic aldehydes and ketones having from 4 to 10 carbon atoms, for instance, heptylaldehyde, cyclohexanone and benzaldehyde;

5. Aliphatic cycloaliphatic and aromatic esters having from 4 to 10 carbon atoms, for instance, isoamylacetate and benzylpropionate;

6. Essential oils or substances containing them, for instance, Ol. eucalypti, Ol. Rutae, cumin oil, limonene, thymol, fenchone and carbone;

7. Halogenated or nitrated aliphatic, cycloaliphatic and aromatic hydrocarbons having 2 to 8 carbon atoms, for instance, hexylbromide, hexylchloride, cyclohexylchloride, benzylchloride, o-dichlorobenzene and nitrocyclohexane; and

8. Mixtures or solutions of all these compounds.

It is to be noted that some of the chlorinated hydrocarbons included under (7) above are toxic or are skin irritants and care should be employed in using them, although they may be of use where an irritant action on the skin is required.

It is to be appreciated that the penetrating effect of the penetrating aids mentioned above is not equal and varies considerably from those which have a strong penetrating effect to those which have a weak penetrating effect, that is to say they require very long periods of contact with the skin to effect penetration.

The active agent of the present preparation for topical application may be a cosmetic agent, a pharmaceutical agent, such as tetracycline, or a dye, or pigment or any other agent which it is desired to introduce into the epidermis. In preparing the preparation, the active agent and penetrating agent are selected preferably so that the active agent is soluble in the penetrating agent, and such that the solution of active agent and penetrating agent is stable. If desired, or if the active agent is not readily soluble in the penetrating agent, a solvent aid may be added which may form part of the carrier.

If it is desired to prepare a non-liquid preparation, such as an ointment, then the above solution can be turned into a jelly or unguent by known pharmaceutical techniques such as by adding a thickener, e.g. fumed silica, or an unguent base. However, it must be borne in

mind that thickeners or unguent bases may reduce the penetration rate, although this may not be of disadvantage if the penetrating aid has such a high rate of penetration that it is desirable to control the rate of penetration.

In general, fatty unguent bases should be avoided as they have an inhibiting effect on the penetrating aid, although, as indicated, they may be useful in controlling the rate of penetration. Thus, it is preferred not to use unguent bases such as liquid paraffin, solid paraffin, petroleum jelly, olive oil, glycerine, *Adeps lanae anhydrous*, lanolin, *Adeps suillus*, stearyl alcohol, cetyl alcohol and zinc ointment bases.

The invention will now be illustrated by the following Examples.

EXAMPLE 1

Malachite green, which is very easy to recognise in the skin as a pigment and which therefore permits of ready histological identification in a frozen section, has strong fungicidal properties ("active principle"). Malachite green dissolved in ethyl glycol does not penetrate the epidermis, but when cyclohexane is used as a penetrating agent in addition to malachite green, which is an aid to solution, malachite green can definitely be detected in deep layers of the skin (corium) after a few minutes. The rate of penetration increases rapidly as the proportion of cyclohexane increases.

EXAMPLE 2

A fluorescing pigment, Rhodamine B, acting as a model for any active principle, is not absorbed from an ethanolic or aqueous solution nor after solution in ethyl glycol, propylene glycol or glycerin. When a penetrating agent is added to these aids to solution, a deep penetration results from a short contact. For instance, if as little as 10% of cyclohexane is added to a Rhodamine B solution in ethyl glycol, the pigment is visible in deep layers of the skin after as little as thirty minutes later. When 50% of cyclohexane is added, Rhodamine is detected in the corium after as little as three minutes; after ten minutes it can be detected even in the subcutaneous fatty tissue.

However, if a mixture of cyclohexanone and Rhodamine B is applied, the Rhodamine

B does not appear in the corium because it is not sufficiently soluble in cyclohexane.

EXAMPLE 3

The following Table lists the results obtained with various penetrating agents:

KEY TO TABLE

| | | |
|-----------|---|----|
| Column 1: | Penetrating agent—substances tested as to their penetrating agent properties. | |
| Column 2: | L% = addition (in percentage by volume) of an aid to solution which has no effect on penetrating properties. Usually ethylglycol (see page 2 of table). | 60 |
| | 50 = 50% of aid to solution. | |
| | — = without any addition. | |
| Column 3: | Active principle: | 65 |
| | Ma = malachite green | |
| | Rh = Rhodamine B | |
| | Or = Orcein | |
| | Mb = Methylene blue | |
| | Su = Sudan III | 70 |
| | Ac = Acridine orange | |
| | Na = Sodium fluorescein | |
| | Fl = Fluorescein | |
| | Eo = Eosin | |
| | Ha = Harmine | 75 |
| | Fu = Fuchsine | |
| | Er = Erythrosine | |
| | Sa = Safranine | |
| | To = Toluidine blue | |
| | Ge = Gentian violet. | 80 |
| Column 4: | t = duration of action in minutes (') or hours (h). | |
| Column: | Epithelium | |
| Column 6: | Hair follicles | |
| Column 7: | Corium | 85 |
| Column 8: | Subcutis | |

HISTOLOGICAL FINDINGS

| | | |
|-----|--------------------------------------|----|
| + | strong colouring or fluorescence | |
| (+) | noticeable colouring or fluorescence | |
| = | slight colouring or fluorescence | 90 |
| — | no colouring or fluorescence | |

There is genuine penetration only when the active principle can be detected in the corium (column 7 or in the subcutis (column 8).

Column 9: Remarks.

The findings were made on guinea pigs unless other wise specified in column 9.

| Penetrating Agent | L % | Active substance | t | Epithelium | Hair shafts | Corium | Subcutis | Remarks |
|-------------------|-----|------------------|-----|------------|-------------|--------|----------|---------|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Methanol | — | Ma | 2h | + | — | — | — | |
| Ethanol | — | Ma | 2h | = | — | — | — | |
| Ethanol | — | Ma | 24h | = | — | — | — | |
| Ethanol | — | Rh | 3 h | = | — | — | — | |
| n-Propanol | — | Ma | 2h | — | — | — | — | |
| i-Propanol | — | Ma | 2h | — | — | — | — | |
| n-Butanol | 50 | Ma | 2h | = | = | — | — | |
| n-Butanol | 50 | Ma | 20h | = | (+) | = | — | |
| i-Butanol | 50 | Ma | 2h | = | = | — | — | |
| tert. Butanol | 50 | Ma | 2h | = | — | — | — | |
| n-Pentanol | 50 | Ma | 2h | (+) | (+) | = | — | |
| i-Amylalcohol | 50 | Ma | 2h | (+) | (+) | = | — | |
| 3-Pentanol | 50 | Ma | 2h | (+) | (+) | = | — | |
| n. prim. Hexanol | 50 | Ma | 2h | + | + | + | = | |
| " | — | Rh | 2h | + | + | + | + | |
| " | — | Rh | 5' | = | = | — | — | Cat |
| " | — | Rh | 30' | (+) | (+) | = | — | Cat |
| " | — | Rh | 2h | + | + | (+) | = | Rabbit |
| " | — | Rh | 30' | (+) | (+) | (+) | = | |
| n-Heptanol | 50 | Ma | 2h | + | + | + | (+) | |
| prim. Octanol | 50 | Ma | 2h | + | + | (+) | = | |
| sec. Octanol | 50 | Ma | 2h | (+) | (+) | = | — | |
| Nonylalcohol | 50 | Ma | 2h | + | + | + | + | |
| Decylalcohol | 50 | Ma | 2h | + | + | + | + | |
| Dodecylalcohol | 50 | Ma | 2h | + | + | + | = | |
| n. prim. | 50 | Rh | 2h | + | + | + | + | |
| Hexene(3)ol(1) | 50 | Rh | 2h | + | (+) | (+) | = | |
| Heptene(3)ol(1) | 50 | Rh | 2h | + | (+) | = | = | |
| Cyclohexanol | 50 | Rh | 2h | (+) | (+) | = | — | |
| Benzylalcohol | 50 | Rh | 2h | (+) | (+) | = | — | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-------------------------------|----|----|-----|-----|-----|-----|---|------------------|
| Phenylmethyl-alcohol | 50 | Rh | 2h | — | — | — | — | |
| Phenylethyl-alcohol | 50 | Rh | 2h | — | — | — | — | |
| Methylglycol | 50 | Rh | 2h | = | — | — | — | |
| Methylglycol | — | Rh | 2h | = | — | — | — | |
| Ethylglycol | — | Ma | 2h | = | — | — | — | |
| „ | — | Ma | 20h | = | = | — | — | |
| „ | — | Rh | 2h | = | — | — | — | see Example 2 |
| „ | — | Rh | 2h | = | — | — | — | Dog |
| „ | — | Rh | 2h | = | — | — | — | Rabbit |
| „ | — | Rh | 2h | — | — | — | — | Cat |
| „ | — | Mb | 2h | — | — | — | — | |
| „ | — | Mb | 6h | — | — | — | — | |
| „ | — | Or | 2h | = | = | — | — | |
| Ethyleneglycol | — | Rh | 2h | — | — | — | — | |
| 1,2-propylene glycol | — | Rh | 2h | = | — | — | — | |
| 1,3-butyleneglycol | — | Rh | 2h | = | — | — | — | |
| Carbitol | — | Rh | 2h | = | = | — | — | |
| Hexamethylene glycol | 50 | Rh | 2h | = | — | — | — | |
| Glycerin | 50 | Rh | 2h | = | = | — | — | |
| Geraniol | 50 | Rh | 2h | — | — | — | — | |
| Linalool | 50 | Rh | 2h | — | — | — | — | |
| Terpinol hydrate | 90 | Rh | 2h | — | — | — | — | |
| Terpineol, thickly viscous | 50 | Rh | 2h | (+) | (+) | = | — | |
| Terpineol, fresh | 50 | Rh | 2h | + | (+) | (+) | — | |
| Menthol | 50 | Rh | 2h | = | = | = | — | |
| Eucalyptol | 50 | Rh | 2h | + | + | (+) | = | |
| Cumin alcohol | 50 | Rh | 2h | = | = | — | — | |
| Anethole | 50 | Rh | 2h | — | — | — | — | |
| Eugenol | 50 | Rh | 2h | — | — | — | — | |
| Isoeugenol | 50 | Rh | 2h | — | — | — | — | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-----------------|----|----|-----|-----|-----|---|---|---|
| Isoeugenol | — | Rh | 2h | — | — | — | — | |
| Carvacrol | 50 | Rh | 2h | — | — | — | — | |
| Apiole | 50 | Rh | 2h | — | — | — | — | |
| Safrol | 50 | Rh | 2h | = | = | — | — | |
| Tinct. Aloes | — | Rh | 2h | = | — | — | — | |
| „ Colocynthid. | — | Rh | 2h | = | — | — | — | |
| „ Cantharidis | — | Rh | 2h | = | — | — | — | |
| „ Capsioi | — | Rh | 2h | = | — | — | — | |
| Spirit. Sinapis | — | Rh | 2h | = | — | — | — | |
| Pentane | 50 | Rh | 2h | + | + | + | + | |
| Hexane | 50 | Rh | 2h | + | + | + | + | |
| Heptane | 50 | Rh | 2h | + | + | + | + | |
| Pentene (2) | 50 | Rh | 2h | + | + | + | + | |
| Hexene (1) | 50 | Rh | 2h | + | + | + | = | |
| Heptene (1) | 50 | Rh | 2h | + | + | + | + | |
| Octene (1) | 50 | Rh | 2h | + | + | + | + | |
| Nonene (1) | 50 | Rh | 2h | + | + | + | + | |
| Decene (1) | 50 | Rh | 2h | + | + | + | + | |
| Cyclohexane | — | Rh | 10' | = | = | = | = | |
| „ | — | Rh | 30' | = | (+) | = | = | |
| „ | — | Or | 30' | = | — | — | — | |
| „ | — | Or | 3h | = | = | — | — | |
| „ | — | Mb | 2h | = | = | — | — | |
| „ | — | Mb | h | = | = | — | — | |
| „ | 20 | Or | 2h | (+) | + | = | = | |
| „ | 25 | Rh | 10' | + | + | + | + | |
| „ | 25 | Rh | 30' | + | + | + | + | |
| „ | 25 | Or | 30' | + | + | = | = | |
| „ | 25 | Or | 1h | + | + | + | + | |
| „ | 25 | Mb | 2h | = | = | = | — | |
| „ | 25 | Ma | 1h | = | (+) | = | — | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-------------|----|----|-----|-----|-----|-----|-----|--------|
| Cyclohexane | 25 | Rh | 30' | + | + | (+) | = | Dog |
| " | 25 | Rh | 30' | + | + | = | = | Cat |
| " | 25 | Rh | 60' | + | + | + | + | Cat |
| " | 40 | Ma | 1h | + | (+) | = | - | |
| " | 50 | Ma | 1h | + | + | + | = | |
| " | 50 | Ma | 2h | + | + | = | = | |
| " | 50 | Su | 2h | + | + | = | = | |
| " | 50 | Or | 1h | + | + | + | = | |
| " | 50 | Ac | 30' | + | + | (+) | = | |
| " | 50 | Ac | 1h | + | + | (+) | = | |
| " | 50 | Na | 30' | + | + | (+) | = | |
| " | 50 | Na | 1h | + | + | + | = | |
| " | 50 | Fl | 30' | (+) | = | - | - | |
| " | 50 | Fl | 1h | (+) | = | (+) | = | |
| " | 50 | Eo | 1h | + | + | + | + | |
| " | 50 | Rh | 2h | = | = | = | - | |
| " | 50 | Rh | 5' | + | + | (+) | (+) | |
| " | 50 | Rh | 10' | + | + | + | + | |
| " | 50 | Rh | 30' | + | + | + | + | |
| " | 50 | Rh | 1h | + | + | + | + | |
| " | 50 | Rh | 30' | + | + | = | = | Dog |
| " | 50 | Rh | 1h | + | + | + | + | Dog |
| " | 50 | Rh | 30' | + | + | = | = | Cat |
| " | 50 | Rh | 10' | (+) | (+) | (+) | (+) | Rabbit |
| " | 50 | Rh | 30' | + | + | + | + | Rabbit |
| " | 50 | Rh | 90' | + | + | + | + | Rabbit |
| " | 50 | Ha | 30' | + | + | (+) | = | Dog |
| " | 50 | Ha | 30' | + | + | (+) | (+) | |
| " | 50 | Ha | 10' | = | = | - | - | |
| " | 75 | Ma | 1h | + | + | + | = | |
| " | 75 | Ma | 2h | + | + | (+) | (+) | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---------------------|----|----|-----|-----|-----|-----|-----|-----|
| Cyclohexane | 75 | Fu | 2h | + | + | (+) | (+) | |
| " | 75 | Er | 2h | + | + | (+) | (+) | |
| " | 75 | Sa | 2h | + | + | (+) | = | |
| " | 75 | Ge | 2h | + | + | (+) | - | |
| " | 75 | To | 2h | + | + | = | = | |
| " | 75 | Or | 30' | + | + | (+) | = | |
| " | 75 | Or | 3h | + | + | + | (+) | |
| " | 75 | Rh | 2' | (+) | (+) | = | - | |
| " | 75 | Rh | 5' | + | (+) | (+) | = | |
| " | 75 | Rh | 10' | (+) | (+) | (+) | (+) | |
| " | 75 | Rh | 30' | + | + | + | + | |
| " | 75 | Rh | 2h | + | + | + | + | |
| " | 75 | Rh | 30' | + | + | = | = | Dog |
| " | 75 | Rh | 30' | + | + | = | | Cat |
| " | 80 | Or | 1h | (+) | + | (+) | - | |
| " | 80 | Rh | 1h | + | + | + | = | |
| " | 90 | Rh | 1h | + | + | (+) | = | |
| Methyl-cyclohexane | 50 | Rh | 2h | + | + | + | + | |
| Benzene | 50 | Rh | 2h | + | + | + | = | |
| Toluene | 50 | Rh | 2h | + | + | + | (+) | |
| Paracymene | 50 | Rh | 2h | + | + | + | = | |
| Cumene | 50 | Rh | 2h | + | + | (+) | = | |
| Limonene | 50 | Rh | 1h | (+) | (+) | = | - | |
| 1,2-diethoxy-ethene | 50 | Rh | 2h | (+) | = | - | - | |
| 1,2-dibutoxy-ethene | 50 | Rh | 2h | + | + | + | + | |
| Hexalkoxy-ethane | 50 | Rh | 2h | - | - | - | - | |
| Dimethoxy-ethane | 50 | Rh | 2h | (+) | = | - | - | |
| Oleum Rutae | 50 | Rh | 1h | + | + | (+) | (+) | |
| Cumin oil | 50 | Rh | 1h | + | + | (+) | (+) | |
| Ol.Menth. | 50 | Rh | 1h | + | + | (+) | (+) | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|----------------------------|----|----|----|-----|-----|-----|-----|---|
| Ol.Eucalypti | 50 | Rh | 1h | + | + | (+) | (+) | |
| Ol.Galangae | 50 | Rh | 1h | + | (+) | = | = | |
| Ol.Tanaceti | 50 | Rh | 1h | (+) | (+) | = | = | |
| Peppermint oil | 50 | Rh | 1h | (+) | (+) | (+) | - | |
| Ol.Camphoric | 50 | Rh | 1h | (+) | (+) | = | = | |
| Ol.Sabinae | 50 | Rh | 1h | = | = | = | = | |
| Ol.Pini sabin | 50 | Rh | 1h | = | = | = | - | |
| Ol.Menth.pip. | 50 | Rh | 1h | (+) | = | = | - | |
| Ol.Terebinth. | 50 | Rh | 1h | (+) | (+) | = | - | |
| „ | 50 | Rh | 2h | + | + | + | (+) | |
| Ol.Juniperi | 50 | Rh | 1h | = | = | = | - | |
| Ol.Petrosel. | 50 | Rh | 1h | = | = | - | - | |
| Ol.Thymi | 50 | Rh | 1h | = | = | - | - | |
| Ol.Balsami } Copaivae } | 50 | Rh | 1h | = | = | - | - | |
| Sassafras oil. | 50 | Rh | 2h | (+) | (+) | - | - | |
| Ol. Anisi | 50 | Rh | 1h | - | - | - | - | |
| Peru balsam | 50 | Rh | 1h | - | - | - | - | |
| Ol.Calami | 50 | Rh | 1h | - | - | - | - | |
| Patchiouli oil | 50 | Rh | 1h | - | - | - | - | |
| Ol.Pagi ethen. | 50 | Rh | 1h | - | - | - | - | |
| Tolu oil. | 50 | Rh | 1h | - | - | - | - | |
| Ol. Pimentae | 50 | Rh | 1h | - | - | - | - | |
| Ol. Origani } orotici } | 50 | Rh | 1h | - | - | - | - | |
| Ajowan oil. | 50 | Rh | 1h | - | - | - | - | |
| Ol. Spicae | 50 | Rh | 1h | - | - | - | - | |
| Thymene(1-Pinene) | 50 | Rh | 1h | + | + | (+) | (+) | |
| α -Pinene | 50 | Rh | 1h | (+) | + | (+) | | |
| Propionaldehyde | 50 | Rh | 1h | = | = | - | - | |
| Butylaldehyde | 50 | Rh | 1h | = | = | - | - | |
| Hexylaldehyde | 50 | Rh | 2h | = | = | = | - | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|-------------------------------------|----|----|----|-----|-----|-----|---|---|
| Heptylaldehyde | 50 | Rh | 2h | = | = | = | = | |
| Octylaldehyde | 50 | Rh | 2h | = | = | - | - | |
| Nonylaldehyde | 50 | Rh | 2h | = | = | - | - | |
| n-capronaldehyde | 50 | Rh | 2h | = | = | - | - | |
| Cyclohexanone | 50 | Rh | 2h | = | = | = | - | |
| Butanone | 50 | Rh | 2h | = | - | - | - | |
| Methylaceto-phenone | 50 | Rh | 2h | = | = | - | - | |
| Methylheptyl-ketone | 50 | Rh | 2h | = | = | = | - | |
| Methylnonyl-ketone | 50 | Rh | 2h | (+) | (+) | = | - | |
| Citral | 50 | Rh | 2h | = | = | - | - | |
| Citronellal | 50 | Rh | 2h | = | - | - | - | |
| Pulegone | 50 | Rh | 2h | (+) | (+) | = | = | |
| Thujone | 50 | Rh | 2h | = | = | = | - | |
| Fenchone | 50 | Rh | 2h | = | = | - | - | |
| Carvon | 50 | Rh | 2h | = | = | = | - | |
| Cumaldehyde | 50 | Rh | 2h | = | = | - | - | |
| Cinnemal | 50 | Rh | 2h | = | - | - | - | |
| Acetone | 50 | Rh | 2h | = | - | - | - | |
| Dioxane | 50 | Rh | 2h | = | - | - | - | |
| Acetylacetate | 50 | Rh | 2h | = | = | - | - | |
| i.amylacetate | 50 | Rh | 2h | (+) | (+) | (+) | - | |
| n-octylacetate | 50 | Rh | 2h | = | = | - | - | |
| Triacetate } glycerol } | 50 | Rh | 2h | = | - | - | - | |
| Acetoacetic acid } ethyl ester } | 50 | Rh | 2h | = | - | - | - | |
| Benzyl acetate | 50 | Rh | 2h | = | = | = | - | |
| Benzyl propionate | 50 | Rh | 2h | (+) | = | - | - | |
| Benzyl butyrate | 50 | Rh | 2h | (+) | = | = | - | |
| Benzyl benzoate | 50 | Rh | 2h | = | = | - | - | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---------------------------------|----|----|----|-----|-----|-----|-----|---|
| Salicylic methyl acid ester | 50 | Rh | 2h | = | = | — | — | |
| Salicylic amyl ester | 50 | Rh | 2h | = | — | — | — | |
| Benzoic acid ethyl ester | 50 | Rh | 2h | = | = | — | — | |
| Phenyl acetic acid methyl ester | 50 | Rh | 2h | = | — | — | — | |
| Phenyl acetic acid ethyl ester | 50 | Rh | 2h | = | — | — | — | |
| Phenylethyl-acetate | 50 | Rh | 2h | = | = | — | — | |
| p-cresolmethyl ether | 50 | Rh | 2h | = | = | = | — | |
| p-cresolethyl-ether | 50 | Rh | 2h | = | = | = | — | |
| Diphenyl ether | 50 | Rh | 2h | = | = | — | — | |
| Dimethyl phthalate | 50 | Rh | 2h | = | — | — | — | |
| Menthyl-valerianate | 50 | Rh | 2h | = | = | = | — | |
| Geranyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Geranyl formiate | 50 | Rh | 2h | = | = | = | — | |
| Geranyl propionate | 50 | Rh | 2h | = | = | = | — | |
| Geranyl butyrate | 50 | Rh | 2h | = | = | — | — | |
| Linalyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Terpinyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Fenchyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Sabinol acetate | 50 | Rh | 2h | = | = | — | — | |
| Bornyl acetate | 50 | Rh | 2h | = | = | — | — | |
| Benzyl cinnamate | 50 | Rh | 2h | = | — | — | — | |
| n-valeric acid diethyl amide | 50 | Rh | 2h | = | — | — | — | |
| Dichloro-ethylene | 50 | Rh | 2h | (+) | (+) | = | = | |
| Trichloroethylene | 50 | Rh | 2h | (+) | (+) | = | = | |
| Tetrachloroethylene | 50 | Rh | 2h | (+) | (+) | = | — | |
| n-allyl bromide | 50 | Rh | 2h | + | + | + | + | |
| n-allyl chloride | 50 | Rh | 2h | + | + | (+) | = | |
| Dibromo ethane | 50 | Rh | 2h | + | + | (+) | (+) | |
| Dichloro ethane | 50 | Rh | 2h | + | + | (+) | (+) | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|----------------------------------|----|----|----|-----|-----|-----|-----|---|
| Tetrachloro-ethane | 50 | Rh | 2h | (+) | (+) | = | = | |
| Tetrabromo ethane | 50 | Rh | 2h | (+) | (+) | = | - | |
| n-butyl bromide | 50 | Rh | 2h | (+) | (+) | = | - | |
| n-amylbromide | 50 | Rh | 2h | (+) | (+) | = | = | |
| sec. amyl bromide | 50 | Rh | 2h | (+) | (+) | (+) | = | |
| n-hexyl bromide | 50 | Rh | 2h | = | + | (+) | (+) | |
| n-heptyl bromide | 50 | Rh | 2h | + | + | (+) | = | |
| n-octyl bromide | 50 | Rh | 2h | (+) | (+) | = | = | |
| i-butylene bromide | 50 | Rh | 2h | (+) | (+) | (+) | - | |
| Cyclohexyl chloride | 50 | Rh | 2h | + | + | + | + | |
| n-dichloro benzene | 50 | Rh | 2h | + | (+) | (+) | (+) | |
| Benzyl chloride | 50 | Rh | 2h | = | = | = | - | |
| 1-chloro-1,2-diethoxyethene | 50 | Rh | 2h | + | + | + | + | |
| 1,2-dichloro-1,2-diethoxy-ethene | 50 | Rh | 2h | + | + | + | + | |
| Ethyl-chlorhydrin | 50 | Rh | 2h | = | - | - | - | |
| Nitromethane | 50 | Rh | 2h | = | - | - | - | |
| Nitroethane | 50 | Rh | 2h | = | - | - | - | |
| 1-nitropropane | 50 | Rh | 2h | = | - | - | - | |
| 2-nitropropane | 50 | Rh | 2h | (+) | - | - | - | |
| Nitrocyclohexane | 50 | Rh | 2h | + | + | + | (+) | |
| α -picoline | 50 | Rh | 2h | - | - | - | - | |
| 2,4-lutidine | 50 | Rh | 2h | - | - | - | - | |
| Paraffinum liquid | 50 | Rh | 2h | = | - | - | - | |
| Yellow paraffin jelly | 50 | Rh | 2h | - | - | - | - | |
| Yellow paraffin oil | 50 | Rh | 2h | - | - | - | - | |
| Oleum Olivarum | 50 | Rh | 2h | = | - | - | - | |
| Ol. Arachidis. | 50 | Rh | 2h | = | - | - | - | |
| Ol. Amygdalarum | 50 | Rh | 2h | = | - | - | - | |
| Ol.Jecoris Aselli. | 50 | Rh | 2h | = | - | - | - | |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|----|----|------|-----|-----|---|---|--------------------|
| Unguent. molle DAB. | — | Rh | 2h | = | = | — | — | |
| Ung. Paraffini | — | Rh | 2h | = | = | — | — | |
| Ung. Glycerin | — | Rh | 2h | (=) | = | — | — | |
| Adeps lanae | — | Rh | 2h | = | = | — | — | |
| Lanolin | — | Rh | 2h | (+) | = | — | — | |
| Tween 20 | 50 | Rh | 2h | = | — | — | — | |
| Tween 80 | 50 | Rh | 2h | = | — | — | — | |
| Squalene | 50 | Rh | 2h | (+) | (+) | — | — | |
| " | 50 | Rh | 1/2h | = | = | — | — | |
| Squalene- (Perhydrosqualene) | 50 | Rh | 1/2h | = | = | — | — | |
| " | 50 | Rh | 1h | (+) | (+) | — | — | |
| " | 50 | Rh | 2h | + | (+) | = | = | |
| Comparison: Cyclohexane | 50 | Rh | 10' | + | + | + | + | |
| Liniment to Federal German Patent Spec. 801,283 | — | Rh | 1h | = | (+) | — | — | |
| Liniment to Federal German Patent Spec. 870,323 | — | Rh | 1h | + | (+) | — | — | thickly viscous |
| " | — | Rh | 1h | + | + | = | — | thinly viscous |

EXAMPLE 4

5 0.5% by weight solution of tetracycline is prepared in a mixture of equal parts by weight of *n*-undecane and ethylene glycol. The resulting lotion is a liquid which can be resorbed through the skin to pass through the epidermis to reach the corium in as short a time as 30 minutes after external application.

EXAMPLE 5

10 50 mg./ml. of fumed silica are added to the preparation of Example 4 to result in a gelatinous ointment which is a semi-solid preparation and from which the tetracycline can be resorbed through the skin very rapidly.

EXAMPLE 6

20 Example 4 is repeated, replacing the ethylene glycol with *n*-docosane, stearyl alcohol or cetyl alcohol all of which have such a strong inhibiting effect on the penetration aid

than no penetration of the tetracycline in the corium could be detected.

EXAMPLE 7

25 A lotion was prepared comprising a 0.5% solution of tetracycline in a mixture consisting of 50% *n*-undecane, 35% ethylene glycol and 15% cetyl alcohol. After external application of this lotion, tetracycline could be detected in the corium, but the rate of penetration was much slower than with the preparation of Example 4.

WHAT I CLAIM IS:—

35 1). An ointment, liniment, lotion or like preparation for topical application, comprising an active agent which is to penetrate the epidermis, and, as an aid for assisting penetration of said active agent into the epidermis, a monovalent saturated or unsaturated aliphatic, cycloaliphatic or aromatic alcohol hav-

ing from 4 to 12 carbon atoms; an aliphatic, cycloaliphatic or aromatic hydrocarbon having from 5 to 12 carbon atoms; a terpene having from 9 to 15 carbon atoms; an aliphatic, cycloaliphatic or aromatic aldehyde, ketone or ester having from 4 to 10 carbon atoms; an essential oil or a substance containing an essential oil; a halogenated or nitrated aliphatic, cycloaliphatic or aromatic hydrocarbon having from 2 to 8 carbon atoms; or a mixture of two or more of such penetration aids, and any inert carrier necessary for forming said preparation, the carrier being such or being present in an amount such as not to prevent penetration by said penetration aid.

2). A preparation as claimed in Claim 1, wherein the preparation also includes a solvent for the active agent and/or penetration aid.

3). A preparation as claimed in Claim 1 or 2, wherein the penetration aid is one which normally has a high rate of penetration into the epidermis, and wherein there is present an inhibitor, which may form part of the carrier, for reducing the rate of penetration.

4). An ointment, linament, lotion or like preparation for topical application in accordance with Claim 1 substantially as hereinbefore described in any one of Examples 1 to 5 and 7 of the foregoing Examples.

THIEMANN, SON & CO.,
Chartered Patent Agents
Prestige House, 14 to 18, Holborn,
London, E.C.1.
Agents for the Applicant.